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SHORT COMMUNICATION

Use of ^{99m}Tc -doxorubicin scintigraphy in females with breast cancer: a pilot study

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Objective: Doxorubicin (Eurofarma, São Paulo, Brazil) is an antitumour agent widely used in the treatment of breast cancer and can be used for tumour tracking when labelled with a radionuclide. Here, we present the results obtained with technetium-99m (^{99m}Tc)-doxorubicin, using the direct method, to evaluate its uptake in breast cancer.

Methods: Four females with confirmed breast carcinoma diagnosis and breast image reporting and data system Category 5 on mammography underwent whole-body and thorax single-photon emission CT/CT imaging 1 and 3 h after ^{99m}Tc -doxorubicin administration.

Results: We observed increased uptake in breast carcinoma lesions and elimination *via* renal and hepatic pathways.

Conclusion: These preliminary results suggest that ^{99m}Tc -doxorubicin may be a promising radiopharmaceutical for the evaluation of patients with breast cancer. Further studies are ongoing.

Advances in knowledge: To our knowledge, this is the first study to evaluate the use of a directly labelled doxorubicin tracer in humans. ^{99m}Tc -doxorubicin could provide information on the response of tumours to doxorubicin.

Breast cancer is the most common cancer in females worldwide, with an estimated 1.67 million new cases in 2012.¹ In order to improve the treatment and prognosis of breast cancer, early detection is extremely important. However, the techniques most often used for cancer evaluation, such as mammography, ultrasonography and MRI, have limitations and are not always capable of differentiating benign from malignant lesions. Breast scintigraphy has some clinical indications and, in association with other imaging methods, can increase the accuracy of diagnoses and reduce unnecessary biopsies.²

Advances in imaging modalities have contributed to the improvement of early breast cancer diagnosis.³ The use of positron emission tomography (PET) and its new radiopharmaceuticals is an important advance in cancer detection.⁴ Hybrid acquisition of PET with CT (PET/CT) allows evaluation of morphological parameters, increasing the sensitivity and specificity of PET findings.⁴ However, the uptake of fluorine-18-fluorodeoxyglucose (^{18}F -FDG), the radiopharmaceutical most often used for PET, changes according to different variables, such as the histological type. In breast cancer, infiltrating ductal carcinoma shows

higher uptake than infiltrating lobular carcinoma, while in ductal carcinoma, uptake is usually low.^{5–7} ^{18}F -FDG uptake also depends on the grade of breast cancer.^{6,8} Hybrid PET/CT has low sensitivity for tumours <1 cm, owing to limitations in spatial resolution and tumour variables,^{7,8} and ^{18}F -FDG uptake may occur in benign lesions such as inflammatory granulomatous mastitis.⁹ Although PET/CT is limited in the evaluation of tumour size and the presence of multifocal disease, this might change with the advent of positron emission mammography (PEM). Eo et al¹⁰ reported that PEM diagnosed more malignant breast lesions than PET/CT, particularly in tumours <2 cm.

Unfortunately, PET scanners are not available in all nuclear medicine services, notably in developing countries. Conventional gamma cameras, on the other hand, are widely available and therefore single-photon emission CT (SPECT) radiopharmaceuticals have the potential to benefit a larger number of patients. Another promising tool is the use of dedicated apparatus for conventional nuclear medicine of the breast, called molecular breast imaging (MBI), which can detect malignant breast lesions <1 cm.^{11,12}

Doxorubicin (Eurofarma, São Paulo, Brazil) is a potent anti-tumour agent that is widely used in chemotherapy for several types of cancer.¹³ It acts by intercalating nucleotide bases, binding to the lipid membrane, and also inhibits the biosynthesis of macromolecules.¹⁴ Among the main side effects of this drug is possible cardiotoxicity.¹⁵ Technetium-99m (^{99m}Tc) is the radionuclide most often used in conventional nuclear medicine; our research group has used ^{99m}Tc to radiolabel different types of cells and molecules.^{16–23} We previously reported a technique for labelling the thymidine precursor thymine with ^{99m}Tc, with good specificity and high predictive value.^{16–18} We have also used ^{99m}Tc-doxorubicin in dogs and cats in order to evaluate its uptake in different kinds of tumours, with promising results, which led to the approval of this pilot trial.²⁴

METHODS AND MATERIALS

Patients

The inclusion criteria consisted of females aged between 18 and 80 years with a confirmed diagnosis of breast carcinoma and breast image reporting and data system (BI-RADS®) Category 5 on mammography, which is characterized by highly suspect mammographic findings, with a 95% probability of malignancy. The patients were previously submitted to a clinical examination, thorax radiography and laboratory tests. Pregnant or nursing patients and those who had undergone previous surgical excision, chemotherapy, hormonal therapy or radiotherapy were excluded. The institutional review board approved the study protocol (No. 188/11–CAAE–0176.0.007.007/11), and fully informed written consent was obtained from all patients.

Labelling methods

Based on a previous experience,²⁴ doxorubicin was labelled with ^{99m}Tc. Briefly, doxorubicin was incubated for 10 min with a reducing agent, and then 370 MBq (10 mCi) of ^{99m}Tc was added. Filtration with a 0.22-mm Millipore filter (EMD Millipore, Darmstadt, Germany) was used to sterilize the radiopharmaceutical. The same amount of doxorubicin (1 ml, at a concentration of 2 mg ml⁻¹) was used in all patients, regardless of weight. This radiolabelling process is under patent.

The radiochemical purity of the compounds was >90%, as tested prior to each injection by instant chromatography. The radiopharmaceutical was injected intravenously in the arm contralateral to the affected breast.

Single-photon emission CT/CT imaging

Planar scans and hybrid SPECT/CT images (BrightView XCT; Philips Healthcare, Best, Netherlands) were acquired 1 and 3 h

after radiopharmaceutical administration, in the following order: (I) whole-body planar for 12 min for the evaluation of the biodistribution, with a 512 × 1024 matrix; (II) CT of the thorax, with a thickness slice of 0.33 mm in a 512 × 512 matrix, for 12 s duration; and (III) SPECT of the thorax, with 64 positions, 30 s each.

Image analysis

The images were analysed independently by two blinded nuclear medicine physicians and were reported according to the uptake concentration in the neoplastic tissue. Breast lesions in scintimammography were classified as positive or negative. Positive lesions referred to lesions showing greater activity than the background. Negative lesions referred to lesions that showed no increase in tracer activity compared with the background.

All patients underwent open surgical biopsy or mastectomy within 2 months of the nuclear medicine procedure.

RESULTS

The radiolabelled molecule showed a labelling efficiency of 92.5% and *in vitro* stability of up to 24 h.

Three of the four patients had ductal breast carcinoma, and one had lobular carcinoma. All carcinomas were invasive, as confirmed by histopathology (Table 1).

Whole-body scintigraphy images obtained 1 h after administration of the radiopharmaceutical demonstrated a physiological distribution in liver and spleen, and a renal elimination. Figure 1 shows representative images from a patient, 1 and 3 h after injection of ^{99m}Tc-doxorubicin, where an increase in liver and spleen uptake was observed.

SPECT/CT images of the thorax indicated uptake of ^{99m}Tc-doxorubicin congruent with the invasive breast tumours. Figures 2 and 3 show representative SPECT/CT images from two patients. ^{99m}Tc-doxorubicin showed uptake in all studied tumours, and the findings of the nuclear medicine physicians coincided. There were no false-positive or false-negative results.

DISCUSSION

In recent decades, different groups have developed radiopharmaceuticals for SPECT imaging, including doxorubicin labelled with tracers. Nuclear medicine has the advantage of allowing the use of small amounts of radiolabelled molecules to non-invasively study their biodistribution *in vivo* without interfering with the process under investigation.²⁵ Even though therapeutic

Table 1. Demographic data

Patient	Age (years)	Carcinoma type	Affected breast	Size of the lesion (cm)
1	62	Ductal	Left	3.5
2	40	Ductal	Right	3.8
3	52	Ductal	Left	1.7
4	41	Lobular	Right	2.1

Figure 1. A 52-year-old patient with a lesion of 1.7 cm in the left breast with a histopathological result of ductal invasive carcinoma. Anterior (a) and posterior (b) whole-body scintigraphy obtained 1 h after administration of ^{99m}Tc -doxorubicin (Eurofarma, São Paulo, Brazil). Anterior (c) and posterior (d) images obtained 3 h after injection of the radiopharmaceutical.

doses of pharmaceuticals may lead to toxicity, the use of small amounts of radiopharmaceuticals is safe, as demonstrated in published studies.²⁶ In the case of doxorubicin, a cumulative dose exceeding 500 mg m^{-2} leads to a chronic heart failure incidence of 26%.²⁷ On the other hand, the use of a lower dose of 240 mg m^{-2} has been reported to lead to chronic heart failure in 0.2–0.9% of patients.^{27,28} In our study, the total amount of doxorubicin administered was <1% of a treatment dose.

Koukourakis et al²⁹ studied the accumulation of ^{99m}Tc -labelled liposomal doxorubicin (Caelyx®, Janssen-Cilag International, USA) in 10 subjects with metastatic brain tumours and 5 patients with brain glioblastoma undergoing radiotherapy. Radiolabelled doxorubicin accumulation was 13- to 19-fold higher in glioblastomas and 7- to 13-fold higher in metastatic lesions than in the normal brain.

Kumar et al³⁰ studied ^{99m}Tc -doxorubicin *in vitro* and in Ehrlich ascites tumour-bearing mice, with a labelling efficiency of 95% and an *in vitro* stability of up to 24 h. Here, we show a labelling efficiency of ^{99m}Tc -doxorubicin, using a direct method, of 92.5% and *in vitro* and *in vivo* stability of up to 24 h. They demonstrated the physiological distribution of ^{99m}Tc -doxorubicin with renal and hepatic clearances. SPECT images were acquired at 1.5, 3 and 4 h in tumour-bearing mice, and a semi-quantitative data analysis showed that a focal concentration of the radiopharmaceutical was seen in the

tumour at 1.5 h, which persisted up to 4 h. In our study, we also observed a rising uptake up to 3 h in patients with confirmed breast cancer.

Bao et al³¹ studied the use of radiolabelled pegylated doxorubicin (Doxil®, Janssen Biotech, Horsham, PA, USA) in normal rats using the compound ^{99m}Tc -N,N-bis(2-mercaptoethyl)-N,N-diethyl-ethylenediamine (^{99m}Tc -BMEDA) and attained an efficiency of $70.6 \pm 8.8\%$, in *in vitro* and *in vivo* studies. The use of BMEDA raises the cost of the procedure, and the pegylated molecule itself is more expensive than the non-pegylated. They observed slow blood clearance and no significant excretion from bowel and bladder in physiological distribution. ^{99m}Tc -Doxil also had a uniformly high uptake level in the bowel and surrounding abdominal tissues at 4, 20 and 44 h.

Yang et al³² evaluated the pharmacokinetics of targeted and untargeted indium-111 (^{111}In)-doxorubicin liposomes after intravenous administration to intracranial human glioblastoma tumour-bearing mice with blood–brain barrier disruption induced by focused ultrasound. The combination of sonication with drugs significantly increased the tumour-to-normal brain doxorubicin ratio.

Labelling doxorubicin with radiopharmaceuticals may also be used to potentiate its effects. After an initial study evaluating the toxicity, dosimetry and therapeutic response of rhenium-186 (^{186}Re)-labelled pegylated liposomal doxorubicin (^{186}Re -liposomal

Figure 2. A 62-year-old patient with ductal carcinoma confirmed by histopathology. Image acquired 1h after administration of ^{99m}Tc -doxorubicin (Eurofarma, São Paulo, Brazil). Tumour uptake is indicated with a red cross. (a) Scintigraphy with ^{99m}Tc -doxorubicin shows uptake in left breast topography. (b) CT image with high density in left breast topography. (c) Fusion of single-photon emission CT (SPECT)/CT images. It is observed that the area with increased uptake in (a) corresponds to the high density in (b). (d) Transversal SPECT, CT and SPECT/CT images.

doxorubicin),³³ Soundararajan et al³⁴ further evaluated the therapeutic efficacy of ^{186}Re -liposomal doxorubicin combined with radiofrequency ablation of human head-and-neck squamous cell carcinoma xenograft in nude rats. Tumour uptake in ^{186}Re therapy groups was studied with small-animal SPECT for 5 days, and therapeutic efficacy was monitored for 6 weeks with measurement of tumour volume, calculation of the percentage injected dose of ^{18}F -FDG in tumour from small-animal PET images, and determination of viable tumour volume at histopathological examination. At 6 weeks after therapy, control of tumour growth was better with ^{186}Re -liposomal doxorubicin than with liposomal doxorubicin alone ($p < 0.01$). The use of

radiofrequency ablation further improved tumour control and viable tumour volume.

Here, we showed that ^{99m}Tc -doxorubicin, labelled by the direct method developed by our research group, was successfully taken up by BI-RADS 5 breast tumours. These results are encouraging for use of ^{99m}Tc -doxorubicin in a study with BI-RADS 3 and 4 lesions. To our knowledge, this is the first study to evaluate the use of a directly labelled doxorubicin tracer in humans. However, our study had limitations, such as the small number of patients. Therefore, larger studies are necessary to determine the potential of ^{99m}Tc -doxorubicin in patients with breast cancer. Another

Figure 3. A 41-year-old patient with lobular carcinoma. Images were acquired 3 h after the administration of ^{99m}Tc -doxorubicin (Eurofarma, São Paulo, Brazil). The lesion uptake is indicated with a red cross. (a) Scintigraphy with ^{99m}Tc -doxorubicin shows uptake in right breast topography. (b) CT image with high density in right breast topography. (c) Fusion of single-photon emission CT (SPECT)/CT images. It can be observed that the area with increased uptake in (a) corresponds to the high density in (b). (d) Transversal SPECT, CT and SPECT/CT images.

possibility to be investigated is imaging ^{99m}Tc -doxorubicin with MBI. Our future direction is to observe, in a larger cohort, which true-positive patients will benefit from doxorubicin therapy in accordance with ^{99m}Tc -doxorubicin scintigraphy.

CONCLUSION

In this preliminary study, the uptake of ^{99m}Tc -doxorubicin proved to be avid to the tumour lesions of the mammary tissue, as confirmed by histopathological studies. We suggest that ^{99m}Tc -doxorubicin might be a potential radiopharmaceutical for

breast tumour imaging. These results encourage us to continue the studies in patients with other BI-RADS categories.

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